Amendments to the Claims

Please amend claims 23 and 38 as indicated in the listing of claims.

Please cancel claim 26 without prejudice or disclaimer.

Please add claims 39-58.

The listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claim 1. (Canceled).

2. (Previously presented) The method of claim 38, further comprising correlating the information with information about a patient from which the sample is obtained.

3. (Original) The method of claim 2, wherein the capture probe is a primary antibody that binds specifically to the protein in the complex.

4. (Previously presented) The method of claim 38, wherein the Raman-active probe construct comprises a secondary antibody as probe and one or more Raman tags.

5. (Previously presented) The method of claim 4, wherein the Raman-active probe construct is a composite organic-inorganic nanoparticle (COIN) with a unique surface enhanced Raman spectroscopy (SERS) signature and the Raman spectrum detected is a SERS spectrum.

6. (Previously presented) The method of claim 38, wherein the proteins are solubilized in an aqueous solution or hydrophilic solvent prior to the separation.

7. (Previously presented) The method of claim 38, further comprising contacting the proteins in the sample with a denaturing agent prior to the separation to obtain denatured proteins.

8. (Previously presented) The method of claim 7, wherein the denaturing agent is selected from a reducing agent, a surfactant, a chaotropic salt, and a combination thereof.

9. (Previously presented) The method of claim 8, wherein the denatured proteins are dried on the substrate prior to the detection of signals.

10. (Previously presented) The method of claim 38, wherein the substrate is coated with one or more organic or inorganic materials prior to immobilization of the proteins thereon

11. (Original) The method of claim 10, wherein the separated proteins are deposited at the discrete locations on the solid substrate by a procedure selected from contact writing, contact spotting, liquid spraying, and dry particle spraying.

12. (Previously presented) The method of claim 38, wherein the separated proteins are deposited without denaturing using wet electrospray deposition.

13. (Previously presented) The method of claim 38, wherein the substrate is aluminum.

14. (Previously presented) The method of claim 38, wherein the substrate is a flat plate.

15. (Previously presented) The method of claim 38, wherein the detecting is automated to accomplish high throughput scanning at a plurality of discrete protein enriched locations.

16. (Previously presented) The method of claim 38, wherein the discrete locations on the substrate comprise a material selected from gold, silver, copper, and aluminum metals, glass, silicon, and ceramic materials.

17. (Previously presented) The method of claim 38, further comprising contacting the proteins at the discrete protein enriched locations with silver nanoparticles, in individual or aggregate forms.

18. (Original) The method of claim 17, further comprising contacting the nanoparticles with at least one chemical enhancer salt.

19. (Original) The method of claim 18, wherein the chemical enhancer salt is LiCl.

20. (Original) The method of claim 17 or 18, wherein the Raman spectra are SERS spectra.

21. (Previously presented) The method of claim 38 or 17, further comprising collecting the Raman spectra or SERS spectra from the discrete protein enriched locations to compile a protein profile of the sample.

22. (Previously presented) The method of claim 21, wherein the collection is automated to accomplish high-throughput SERS spectra screening of the discrete protein enriched locations.

23. (Currently amended) The method of claim 38, wherein the Raman spectra and locations of the proteins on the solid substrate ~~or within the at least one stream of flowing liquid~~ are recorded and correlated.

24. (Previously presented) The method of claim 38 or 22, wherein the spectrum contains information regarding a protein characteristic selected from a chemical bond, residue composition, residue structure, relative positions of residues, identity of the protein, and combinations thereof.

25. (Previously presented) The method of claim 38, wherein step b) includes maintaining the separated proteins in a separated state.

Claim 26. (Canceled)

27. (Previously presented) The method of claim 38, further comprising analyzing the separated proteins by mass spectroscopy to identify one or more functional groups contained within a separated protein or fragment thereof.

28. (Original) The method of claim 27, further comprising compiling data obtained from the Raman spectra or SERS spectra with data obtained from the mass spectroscopy.

29. (Previously presented) The method of claim 38 or 28, wherein the sample is a patient sample.

30. (Original) The method of claim 29, wherein the patient sample is a body fluid selected from urine, blood, plasma, serum, saliva, semen, stool, sputum, cerebral spinal fluid, tears, and mucus.

31. (Previously presented) The method of claim 38 further comprising creating a protein profile of the sample based on data obtained from the Raman spectra and/or the SERS spectra.

32. (Original) The method of claim 31, further comprising repeating the method using a variety of different patient samples to create a protein library containing a plurality of different protein profiles.

33. (Original) The method of claim 32 further comprising comparing the protein profile of the sample with one or more protein profiles of the library to detect a difference, wherein the difference is indicative of a disease in the patient.

Claims 34-37. (Canceled)

38. (Currently amended) A method for analyzing protein content of a complex biological sample, comprising:

a) chromatographically separating proteins and protein fragments in the sample into a plurality of fractions, each fraction containing an individual protein or protein fragment;

b) depositing each fraction at a discrete location on a solid substrate ~~or within at least one stream of flowing liquid in a microfluidic system~~ to create a plurality of discrete protein enriched locations, thereby maintaining the chromatographically separated proteins and protein fragments in a separated state;

c) contacting the separated proteins deposited at the plurality of discrete protein enriched locations with probes under conditions suitable to form a capture probe/protein complex at one or more of the discrete protein enriched locations;

d) contacting the complexes with a Raman-active probe construct that binds to the protein or the complex; and

e) detecting Raman spectra produced by the probe construct/protein complexes at the plurality of discrete protein enriched locations, wherein a Raman spectrum at a selected one of the plurality of discrete protein enriched locations provides information about a chemical

composition of a protein deposited at the selected discrete protein enriched location, thereby analyzing the protein content of a complex biological sample.

39. (New) A method for analyzing protein content of a complex biological sample, comprising:

a) chromatographically separating proteins and protein fragments in the sample into a plurality of fractions, each fraction containing an individual protein or protein fragment;

b) depositing each fraction at a discrete location within at least one stream of flowing liquid in a microfluidic system to create a plurality of discrete protein enriched locations, thereby maintaining the chromatographically separated proteins and protein fragments in a separated state;

c) contacting the separated proteins with probes under conditions suitable to form a capture probe/protein complex at one or more of the discrete protein enriched locations;

d) contacting the complexes with a Raman-active probe construct that binds to the protein or the complex; and

e) detecting Raman spectra produced by the probe construct/protein complexes at the plurality of discrete protein enriched locations, wherein a Raman spectrum at a selected one of the plurality of discrete protein enriched locations provides information about a chemical composition of a protein deposited at the selected discrete protein enriched location, thereby analyzing the protein content of a complex biological sample.

40. (New) The method of claim 39, further comprising correlating the information with information about a patient from which the sample is obtained.

41. (New) The method of claim 40, wherein the capture probe is a primary antibody that binds specifically to the protein in the complex.

42. (New) The method of claim 39, wherein the Raman-active probe construct comprises a secondary antibody as probe and one or more Raman tags.

43. (New) The method of claim 42, wherein the Raman-active probe construct is a composite organic-inorganic nanoparticle (COIN) with a unique surface enhanced Raman spectroscopy (SERS) signature and the Raman spectrum detected is a SERS spectrum.

44. (New) The method of claim 39, wherein the detecting is automated to accomplish high throughput scanning at a plurality of discrete protein enriched locations.

45. (New) The method of claim 39, further comprising contacting the proteins at the discrete protein enriched locations with silver nanoparticles, in individual or aggregate forms.

46. (New) The method of claim 39, further comprising collecting the Raman spectra or SERS spectra from the discrete protein enriched locations to compile a protein profile of the sample.

47. (New) The method of claim 46, wherein the collection is automated to accomplish high-throughput SERS spectra screening of the discrete protein enriched locations.

48. (New) The method of claim 39, wherein the Raman spectra and locations of the proteins within the at least one stream of flowing liquid are recorded and correlated.

49. (New) The method of claim 39, wherein the spectrum contains information regarding a protein characteristic selected from a chemical bond, residue composition, residue structure, relative positions of residues, identity of the protein, and combinations thereof.

50. (New) The method of claim 39, wherein step b) includes maintaining the separated proteins in a separated state.

51. (New) The method of claim 39, further comprising mixing the stream of flowing liquid comprising the separated proteins with a stream of flowing liquid comprising metal colloids by combining the streams under conditions suitable for contacting the separated proteins with the metal colloids and the detection is SERS detection.

52. (New) The method of claim 39, further comprising analyzing the separated proteins by mass spectroscopy to identify one or more functional groups contained within a separated protein or fragment thereof.

53. (New) The method of claim 52, further comprising compiling data obtained from the Raman spectra or SERS spectra with data obtained from the mass spectroscopy.

54. (New) The method of claim 53, wherein the sample is a patient sample.

55. (New) The method of claim 54, wherein the patient sample is a body fluid selected from urine, blood, plasma, serum, saliva, semen, stool, sputum, cerebral spinal fluid, tears, and mucus.

56. (New) The method of claim 39 further comprising creating a protein profile of the sample based on data obtained from the Raman spectra and/or the SERS spectra.

57. (New) The method of claim 56, further comprising repeating the method using a variety of different patient samples to create a protein library containing a plurality of different protein profiles.

58. (New) The method of claim 57 further comprising comparing the protein profile of the sample with one or more protein profiles of the library to detect a difference, wherein the difference is indicative of a disease in the patient.